the adult respiratory distress syndrome. The control group was treated with mechanical ventilation and positive end-expiratory pressure. The result in both groups was about 10% survival, leading to the conclusion that extracorporeal membrane oxygenation has no role in this disorder. In the early 1980s, neonatologists had better success in the treatment of neonatal respiratory distress syndrome, with an overall survival rate reaching 78%.

Several recent European reports have suggested that the survival rate for patients treated with extracorporeal membrane oxygenation who met the entry criteria of the original 1974 study was close to 50%, reviving interest in lung-assist devices. There have been several important improvements in the technology, such as thromboresistant coating of the surfaces used, improved efficiency of membranes, and better pumps to reduce hemolysis and platelet destruction. The major change was that extracorporeal membrane oxygenation was modified into extracorporeal CO_2 removal. In the former procedure, blood completely bypasses the heart and the lungs. This technique is designed to support the failing lungs and heart. In extracorporeal CO_2 removal, blood is drained from and returned to the vena cava after membrane gas exchange, therefore only supporting the lungs. Extracorporeal CO_2 removal also allows the use of low-frequency mechanical ventilation, low positive end-expiratory pressure, and continuous low-flow oxygen, but oxygen uptake continues to occur mainly in the lungs. The technique is labor intensive, requires capital equipment, and runs at high cost.

The intravascular oxygenator is an intracorporeal gas-exchange device placed in the vena cava. It is constructed with polypropylene hollow fibers coated with ultrathin biocompatible siloxane. All blood-contacting surfaces are also coated with covalently bonded heparin. Oxygen is sucked through the fibers, gas exchange occurs through the membranes, and blood is oxygenated intravenously. Placement and maintenance are relatively simple and inexpensive. Because of its relatively small surface area, its capacity is only a third to half of the gas exchange necessary to maintain aerobic metabolism.

Thus, extracorporeal membrane oxygenation is an acceptable technique in the management of neonates with respiratory distress syndrome. In adults, all three techniques are still experimental but have promise. The development of a totally artificial lung remains some time away.

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Bronchiolitis Obliterans Organizing Pneumonia

THE TERM bronchiolitis obliterans organizing pneumonia (BOOP) was coined in 1985 to describe a lung disease characterized histologically by the presence of intraluminal fibroblastic proliferation. In Europe, BOOP is also known as cryptogenic organizing pneumonitis. It has recently been suggested that the disorder be renamed as cryptogenic intramural fibrosis of distal air spaces.

Bronchiolitis obliterans organizing pneumonia is divided into primary or idiopathic and secondary. The secondary BOOP may occur in association with certain infections—with *Legionella, Mycoplasma,* or *Adenovirus* species—the inhalation of toxic gases (nitrogen dioxide), graft-versus-host disease in bone marrow and heart-lung transplant recipients, and collagen vascular diseases. It is, however, the idiopathic or primary BOOP that enters in the differential diagnosis of diffuse interstitial lung disease.

Because of certain common clinical and physiologic abnormalities, BOOP is often misdiagnosed as idiopathic pulmonary fibrosis, sarcoidosis, pneumoconiosis, hypersensitivity pneumonitis, or chronic eosinophilic pneumonia. It is important that BOOP, because of its benign course and favorable response to corticosteroids, is not overlooked or misdiagnosed.

Idiopathic BOOP occurs mainly in adults, with a peak incidence in the sixth decade; women and men are affected equally. Most patients have a subacute illness with cough, dyspnea, fever, and fatigue of a few weeks' duration. The patient's sedimentation rate is often elevated. Although auscultation may reveal rales, in a third of patients the results of a pulmonary examination are normal. Hypoxemia occurs in almost all patients. Lung volumes are reduced, but airway obstruction is not a feature. Diffusing capacity is impaired. Chest roentgenograms show bilateral patchy airspace densities, commonly in peripheral areas, and many other radiographic patterns have also been reported. Honeycombing is rare. The conventional and high-resolution computed tomographic scan findings are nonspecific, but these new techniques are helpful in distinguishing BOOP from idiopathic pulmonary fibrosis and granulomatous lung disease. On histologic examination, the lungs display immature-appearing plugs in the respiratory bronchioles, alveolar ducts, and peribronchial alveolar spaces. The alveolar spaces also contain foamy cells reflecting the proximal airway obstruction. Alveolar septa are thickened and contain mononuclear cell infiltrate. The presence of intraluminal plugs of fibroblasts, however, distinguishes BOOP not only from idiopathic pulmonary fibrosis but also from other interstitial lung disorders.

When should a clinician think about a diagnosis of bronchiolitis obliterans organizing pneumonia? Internists and pulmonologists should consider including BOOP in the differential diagnosis of a subacute interstitial pneumonia, particularly when the patient has influenza-like features with cough, dyspnea, fever, malaise, and weight loss. A poor or unsatisfactory response to antibiotics is another feature favoring this diagnosis. A good transbronchial lung biopsy specimen in conjunction with a strongly suggestive clinical history and examination is in many cases adequate to establish the diagnosis. An open-lung biopsy is needed when a transbronchial biopsy fails to establish the diagnosis. This pneumonia has an excellent prognosis. It responds well to corticosteroids; almost two thirds of the patients in one study improved with the use of corticosteroids. Fewer than 5% of patients die of respiratory failure.

Idiopathic bronchiolitis obliterans organizing pneumonia was recently added to the long list of interstitial disorders. The disease has a benign course with an excellent response to corticosteroids, but we remain ignorant of its cause.

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Advances in Pulmonary Biopsy Techniques

IN THE PAST DECADE, refinements in transthoracic and transbronchial fine-needle aspiration (FNA) techniques, the introduction of thoracoscopic biopsies, and the improvement in lesion imaging and specimen processing have led to a continued decline in the need for open lung biopsies.

The main indications now for percutaneous transthoracic FNA are the biopsy of pulmonary nodules and aspiration of infectious lesions. The diagnostic yield of conventional transbronchial forceps biopsy diminishes with the size of the lesion, whether infectious or neoplastic, so that lesions less than 2 cm to 3 cm are best approached by FNA. In immunocompromised patients, in whom early diagnosis is paramount, small subsegmental and peripheral lesions should undergo FNA under computed tomographic or fluoroscopic guidance because a positive result provides both a diagnosis and confirmation of invasion for otherwise potentially saprophytic organisms like fungi.

Transbronchial FNA by flexible bronchoscopy has the advantage of a lower risk of pneumothorax than percutaneous methods. Its 50% yield in peripheral lesions supplements conventional transbronchial forceps biopsy, washing, and brushing, so that using them together increases the overall yield to about 70%. Compared with transbronchial forceps biopsy, transbronchial FNA is a better technique for metastatic lesions because these tend not to be peribronchial in distribution and hence require deeper biopsies. In addition, about 50% to 60% of malignant mediastinal lymph nodes in paratracheal, subcranial, and aorticopulmonary sites can be sampled with transbronchial FNA guided by computed tomographic images. When successful in the evaluation of lung cancer, this method provides both a cytologic diagnosis and staging, without the need for mediastinoscopy. Because transbronchial FNA has only moderate sensitivity, a negative result does not rule out malignant adenopathy, and it should be noted that the method provides no information about whether disease has spread through the involved node's capsule, a known factor in prognostication. Other uses of transbronchial FNA include the biopsy of extrabronchial compressive lesions and superficially necrotic tumors that require deeper biopsies.

Newer molecular biology and immunohistologic tools have partially eliminated the need for the larger biopsies obtainable only by thoracotomy. Immunohistologic methods using antibodies directed against cell surface antigens can usually separate, for example, reactive lymphocytosis from lymphoma. Gene rearrangement techniques are so sensitive that even cytologic specimens obtained by bronchoalveolar lavage may be adequate for diagnosing certain lymphomas. A polymerase chain reaction assay for *Mycobacterium tuberculosis* holds similar promise for very small or even expectorated specimens in tuberculosis.

When large pleural or parenchymal specimens are required, diagnostic thoracoscopy is now an option. Under general anesthesia, a double-lumen tube is placed to permit collapse of the lung. A rigid thoracoscope is inserted by trocar for plain or video viewing. An operating probe or second thoracoscope, which can incorporate the use of therapeutic carbon dioxide or neodymium-yttrium-aluminum-garnet lasers, is positioned separately to permit wedge excisional biopsy or even segmentectomy. In pleural diseases, thoracoscopy has proved invaluable in diagnosis, and in appropriate cases, therapeutic pleural debridement and even ablation of pleural blebs can be accomplished using these techniques.

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Lung Transplantation

HUMAN LUNG transplantation actually predated heart transplantation, beginning with a single-lung transplant done in 1963. Over the next 15 years, about 44 single-lung transplants were attempted worldwide. The results were uniformly dismal, however, and the procedure was abandoned. Studies of animals suggested that en bloc transplantation of the heart and both lungs provided better vasculature to the tracheobronchial tree, leading to the first successful human heart-lung transplant at Stanford University Medical Center in 1981. This procedure is successful for combined cardiopulmonary disease, particularly congenital heart disease and right ventricular failure associated with pulmonary hypertension. Combined heart-lung blocks are in limited supply, however, stimulating efforts to use lung-only grafts.

Single-lung transplantation was successfully reintroduced in 1983. Major principles advocated were selecting recipients with fibrotic disease only; wrapping the bronchial anastomosis with omentum; not giving preoperative corticosteroids; and avoiding administering maintenance corticosteroids in the early postoperative period. Over the past five years the original principles have been progressively modified: Single-lung transplantation is appropriate for patients with fibrotic disease, emphysema, and perhaps pulmonary hypertension; omental wrapping of the bronchial anastomosis is not required; patients may be successfully transplanted while receiving low dosages of corticosteroids; and instituting corticosteroid therapy immediately following transplantation may be acceptable.

Double-lung transplantation was introduced in 1986. The original procedure involved a low tracheal anastomosis and was technically flawed, with a high rate of tracheal dehiscence. It has now been replaced with bilateral bronchial anastomoses with improved results.

The results of lung and heart-lung transplantation continue to improve with one- and five-year survival rates approaching 75% and 50%, respectively. Candidates for transplantation should have a life expectancy of less than 2 to 3 years without transplantation and be otherwise healthy. Most programs set age limits for transplantation, such as age 60 for single lung, age 50 for double lung, and age 45 for heart-lung transplantation. Rejection monitoring requires frequent assessment of pulmonary function along with bronchoscopy and transbronchial biopsy. The long-term immunosuppression regimen consists of cyclosporine, azathioprine, and prednisone.

Long-term immunosuppression places transplant patients at risk for various unusual infections. In addition, oblitera-